Conferences and Reviews

Overwhelming Postsplenectomy Infection
Still a Problem

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Despite an extensive medical literature over the past ten years, patients continue to die needlessly of overwhelming postsplenectomy infection. Although physicians have become increasingly cognizant of this syndrome in children, many remain unaware of the risk to asplenic or hyposplenic adults with no underlying medical problems. In addition, many older asplenic or functionally hyposplenic persons are unaware that they are at risk for this syndrome. The identification of Howell-Jolly bodies on a peripheral blood smear should alert physicians to the need for further follow-up to establish hyposplenism and to consider possible antipneumococcal vaccination.

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A 36-year-old man presented to an emergency department at 6:30 PM with a half-day history of flulike symptoms. There was a history of splenectomy at age 5½ because of hereditary spherocytosis. The patient had not received the pneumococcal vaccine. He appeared fine on leaving for work at 6 AM, but came home at 1:30 PM complaining of feeling poorly with malaise and myalgias. By 3:30 PM the patient was febrile (39.5°C) with vomiting, diarrhea, and lower back pains.

In the emergency department, the patient was hypotensive and oliguric with a blood pressure of 80/40 mm of mercury and a temperature of 40°C. On examination he was mentally confused and appeared "shocky" and cyanotic with several large purpura on the trunk and petechiae on both lower extremities. A blood gas determination documented metabolic acidosis, and hematologic investigations suggested the presence of disseminated intravascular coagulation. A tentative diagnosis of septic shock due to postsplenectomy infection was made. Vigorous treatment with hydration, large doses of penicillin, steroids, a dopamine infusion, and blood component therapy was promptly instituted. Despite these therapeutic measures, the patient died three hours after hospital admission. Autopsy findings were compatible with the Waterhouse-Friderichsen syndrome, and all antemortem blood cultures subsequently showed *Streptococcus pneumoniae*.

Clinical Features and Incidence

The common clinical features of overwhelming postsplenectomy infection (OPSI) are outlined in Table 1.[1-4] As the case history illustrates, few infectious states can proceed as rapidly in apparently healthy persons. Although meningitis or pneumonia may accompany OPSI, in many patients there is no obvious site of bacterial colonization, and a cryptic source in the nasopharynx is frequently postulated. The initial prodrome is typically mild and nonspecific with flulike symptoms. These may include fever, malaise, myalgias, headache, and vomiting. This initial prodrome is usually followed by a rapid evolution to full-blown bacteremic septic shock accompanied by hypotension, anuria, and clinical evidence of disseminated intravascular coagulation. Severe hypoglycemia may be present. The subsequent clinical course frequently mirrors that of the Waterhouse-Friderichsen syndrome, and bilateral adrenal hemorrhages may be found at autopsy. Despite intensive therapeutic intervention, the overall mortality as published in older studies for establishing cases varied from 50% to 70%.[1] More recent information suggests that if informed patients seek medical attention promptly, mortality may be reduced to the 10% range.[5] Of those patients who die, more than 50% do so within 48 hours of admission to hospital.[1]

The infecting organisms characteristically are encapsulated.[1-3] The organism most frequently implicated has been the pneumococcus (*S pneumoniae*). This organism has been implicated in roughly half of all reported cases. *Haemophilus influenzae*, meningococcus (*Neisseria meningitidis*), and group A streptococci have accounted for an additional 25% of infections. Less frequent pathogens include *Staphylococcus* species, *Pseudomonas* species, or other gram-negative organisms.[3] Recently the fastidious bacterium DF-2 (*Capnocytophaga canimorsus*) has been identified as a pathogen responsible for OPSI following dog bites.[6] Frequently bacterial proliferation in OPSI is so extreme that bacteria may be seen in buffy-coat preparations or remarkably in the polymorphonuclear leukocytes present on smears made from unspun peripheral blood.[7] The precise incidence of OPSI remains controversial because published estimates vary considerably. The most reliable data, reported by Schwartz and co-workers, were derived by applying actuar-

TABLE 1.—*Clinical Features of Overwhelming Postsplenectomy Infection*

Cryptic infection (no obvious focus)
Short, nonspecific prodrome
Massive bacteremia with encapsulated organism
Septic shock with disseminated intravascular coagulation
Marked virulence: 50% to 70% mortality
Death ensues in 24 to 48 hours

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ial methods to a population free of selection bias and with accurate long-term follow-up.[8] This study estimated that the risk of fulminant infection was reasonably low, in the range of 1 case per 500 person-years of observation. The overall cumulative risk of infection requiring admission to hospital, however, was 33% by the end of a ten-year follow-up after splenectomy. Following splenectomy in childhood, the incidence is probably greater, in the range of 1 fatal case of OPSI for 300 to 350 patient-years of follow-up.[1] Because most of the published data antedate the availability of the pneumococcal and *H influenzae* vaccines, the current overall incidence of OPSI is likely to be lower than these published estimates.[2,3]

Factors Predisposing to Overwhelming Infection

The single most important factor in the pathophysiology of OPSI appears to be the vital role of splenic macrophages in dealing with encapsulated organisms.[1,2] It is clear from the medical literature, however, that the predisposition of asplenic and hyposplenic persons to infection varies with the patient population examined and the underlying disease status.[3]

The age at which splenectomy occurs is an important consideration.[1-3] Although adults are not immune from OPSI, children are clearly at greater risk, especially those younger than 2 years. This is probably related to the fact that the coating of bacteria with opsonizing antibodies and the tortuous splenic microcirculation are key factors in the effective phagocytosis of encapsulated organisms. Infants do not acquire specific antibodies against encapsulated organisms until relatively late in the development of the normal range of antibody responses.

The reason for splenectomy also appears to be a key factor.[1,2] Splenectomy performed for a hematologic disorder or lymphoma appears to carry a much higher risk than splenectomy performed as a result of trauma. Although part of this may be related to the immune status of the patient, a major factor is probably the occurrence of splenic implants (splenosis) or accessory spleens in traumatized patients.

The time interval from the date of splenectomy is also important. Several studies have shown that most admissions to hospital for serious infections occur within the first two years.[4] For instance, in young children who have had a splenectomy, 80% of OPSI cases occur within this time frame. It must be emphasized, however, that some degree of risk persists for all of adult life. There are case reports of OPSI occurring as long as 42 years after a splenectomy.[9]

The presence of splenic implants or accessory spleens is also a major risk modifier. Small implants of splenic tissue in the peritoneum are found in about 50% of patients who undergo splenectomy for trauma, an event known as splenosis.[2,3] About 10% of these patients have accessory spleens. There is both experimental and clinical evidence that regenerative splenic tissue can be protective even if the amount of residual tissue is only a small fraction of the normal organ mass.[10] The degree of protection appears to be variable and unpredictable, however. A number of reported cases of OPSI have occurred in the face of remaining splenic tissue or splenic implants.[11]

The overall immune status of a person is also important.[1-3] Conditions that are known to be associated with defects in cellular or humoral immunity such as Hodgkin's disease or hypogammaglobulinemia can have a major effect on a person's ability to mount an effective antibody response to foreign antigens or infection.

Identifying Risk in Patients

Although patients who are known to have had a splenectomy for hematologic disease or trauma may be readily apparent, there exists a population of persons who suffer from functional hyposplenism or may not be aware that their spleens were removed during gastric or hiatal hernia repair.[3] In addition, although rare, the spleen may be congenitally absent, especially in association with certain cardiac malformations.[1]

The wide variety of diseases that have been linked with functional hyposplenism is shown in Table 2.[1-3] Although many of these conditions are rare, certainly the association in some patients with relatively common conditions such as severe liver disease, celiac disease, ulcerative colitis, or systemic lupus erythematosus merits clinical attention. In addition, patients undergoing high-dose steroid therapy or splenic irradiation as part of cancer therapy may have impaired splenic phagocytic activity and face an increased risk for OPSI.[12] Functional hyposplenism has also been reported as a late complication of allogeneic bone marrow transplantation complicated by extensive graft-versus-host disease.[13]

TABLE 2.—*Conditions That May Be Associated With Hyposplenism*

Type	*Disorder*
Gastrointestinal	Celiac sprue
	Dermatitis herpetiformis
	Ulcerative colitis
	Liver disease—portal hypertension
Immunologic	Systemic lupus erythematosus
	Rheumatoid arthritis
	Graves' disease
	Polyarteritis nodosa (splenic infarct)
Infiltrative	Thorium dioxide (Thorotrast) administration
	Amyloidosis
	Sarcoidosis
Miscellaneous	Sickle cell disease
	After bone marrow transplantation
	Cancer therapy
	?High-dose steroid therapy
	?Splenic irradiation

Fortunately, a hematology laboratory can play a major role in identifying patients at risk. A consistent abnormality reflecting hyposplenism or asplenia is the presence of Howell-Jolly bodies.[3] These small, round remnants of the original erythrocyte nucleus are readily apparent on microscopic examination of a peripheral blood smear (Figure 1). Although some of the newer automated hematology analyzers may on occasion flag Howell-Jolly bodies, if any question of asplenia or hyposplenism exists, the clinician should always request a standard blood smear review. The finding of Howell-Jolly bodies in a peripheral blood smear, although not sufficiently sensitive for the detection of minor degrees of hyposplenism, can identify a degree of hyposplenism that presents a risk for OPSI.[14] One reference laboratory processing more than 100,000 peripheral blood smears per year reported an incidence of new patients showing Howell-Jolly bodies of 1 per 200 or 0.5%.[15] Many of these patients and their physicians were unaware of their asplenia or hyposplenism. When Howell-Jolly bodies are noted on a peripheral smear, the laboratory should clip a note to the report

form informing the patient's physician of the possible presence of hyposplenism. Practicing physicians in turn must be alert for the appearance of Howell-Jolly bodies and follow up on any patients in whom this abnormality is reported for asplenia or functional hyposplenism. If any question exists as to the physical presence or functioning of the spleen, a radionuclide spleen-liver scan may be of benefit.

Measures to Prevent Overwhelming Infection

With a growing appreciation of OPSI, splenic surgery has become increasingly conservative.[16] The trend seems to be to avoid splenectomy whenever possible by observing patients with confirmed isolated splenic rupture and using blood transfusions appropriately. In one such protocol, surgery is not done if the hematocrit becomes stable during the first 24 hours and transfusion requirements do not compromise more than a third of the blood volume.[17] New surgical procedures such as splenorrhaphy or partial splenectomy have been developed that will often allow the spleen to be preserved or repaired.[18] Another surgical approach is splenic autotransplantation into the mesentery, but the overall effectiveness of this procedure is still being evaluated.[19]

A major breakthrough in the prophylaxis of patients at high risk for OPSI has been the introduction of an effective

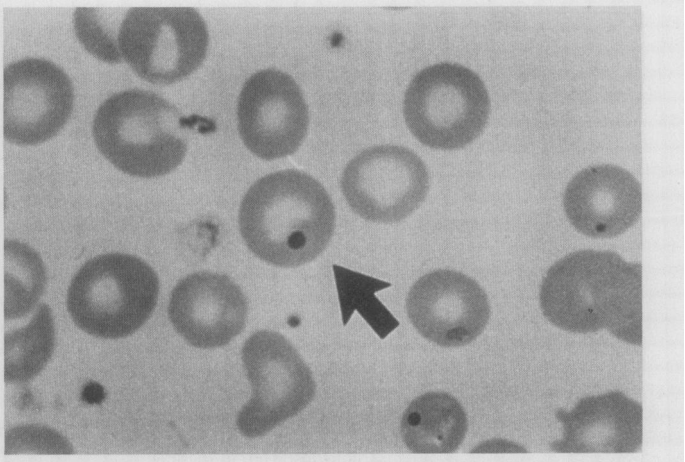

Figure 1.—The presence of Howell-Jolly bodies (arrow) on the peripheral blood smear is suggestive of asplenia or hyposplenism.

polysaccharide vaccine for *S pneumoniae*.[20] This vaccine currently contains purified capsular material from 23 of the most prevalent types of *S pneumoniae*. It has been estimated that these 23 bacterial types are responsible for 90% of the bacteremic pneumococcal disease seen in North America.[21] Because the vaccine comprises 23 independent polysaccharide antigens, about 10% of possible antibody responses to individual antigens unfortunately do not occur. This partially explains the fact that cases of OPSI have occurred in those who have received the vaccine.[22] Young children, persons with neoplastic disease, and those who are immune compromised or receiving immunosuppressive therapy are the least likely to be protected by the vaccine.[23] For instance, new patients with Hodgkin's disease should be vaccinated at least two weeks before therapy to allow for an adequate antibody response. If vaccination is delayed until after treatment has begun, inadequate antibody responses are observed for as long as three years.[24]

The administration of the pneumococcal polysaccharide vaccine appears to carry minimal morbidity.[20] Vaccination should not be done during a febrile illness. In a pregnant woman, vaccination should generally be deferred, and in any patient the possible risks of infection should be weighed against any possible hazards associated with the vaccine. About 30% of patients have minor side effects including erythema, myalgia, or mild induration with localized pain at the injection site; 3% to 7% of patients have mild pyrexia for 24 to 48 hours after vaccination. Severe systemic reactions with photophobia, chills, and high fever occur with only 1 in 1,000 vaccinations and usually resolve spontaneously. The duration of protective antibody levels is at least three to five years in most nonimmunosuppressed persons.[20]

The official recommendation for most patients had been for a single pneumococcal vaccination because of an increased incidence of local reactions initially reported following revaccination. Recent guidelines, however, have suggested that high-risk patients such as those without spleens should now be considered for revaccination after three to six years. This is especially the case if they received the earlier 14-valent vaccine rather than the current 23-valent preparation or there is reason to suspect that their antipneumococcal antibody levels have declined substantially.[25]

Most recently vaccines for *H influenzae* and meningococcus groups A and C have become available. Some authorities have also advocated providing these on a routine basis to all asplenic or functionally hyposplenic younger patients.[26,27] Unfortunately, the protective efficacy of these vaccines has not been as great as that associated with the use of the pneumococcal vaccine, and most trials have been in healthy persons rather than patients undergoing splenectomy.[28]

As noted earlier, sporadic cases of pneumococcal vaccine failure have been reported in appropriately immunized persons. In addition, other bacteria account for at least 50% of OPSI cases. For these reasons, vaccination by itself should not confer a false sense of security. Besides vaccination, patients who have lost their spleens or have functional hyposplenism must be made aware of the possibility of OPSI. The advice given should be simple, clear, and nonalarmist.[29] All such persons should wear a Medic Alert bracelet* detailing their condition.

Patients should be advised that if they become acutely ill, they should report symptoms that might otherwise be dismissed as "the flu" to their physicians.[1,2] In this situation, a possibility is to admit such patients to the hospital immediately and obtain appropriate cultures. While the microbiology status remains uncertain, intravenous antibiotic therapy could be commenced, or as an alternative, the patient may be closely observed.[3] If it is elected to use antibiotics, penicillin is probably the drug of choice for adults, in whom *S pneumoniae* or *N meningitidis* is frequently responsible for infection. Another drug such as ampicillin or a third-generation cephalosporin would be required for children in whom *H influenzae* or gram-negative organisms may be present. If no evidence of progressive infection is noted and microbiologic workup is negative, the patient may be discharged after an observation period of 8 to 12 hours.

Some authors have advocated giving patients their own supply of an antibiotic such as ampicillin, to be taken at the first sign of a respiratory illness, fever, or rigor, especially if there is likely to be any delay in medical evaluation.[30] There is currently no definite proof that such early treatment will

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lower the incidence of OPSI.[1,2] The literature series with the lowest mortality reported to date emphasized patient education, close follow-up, and prompt medical advice at the earliest sign of even minor infection.[5]

A suggestion has also been made that prophylactic ampicillin therapy be given twice a day for two years or longer to all patients immediately after they have had a splenectomy.[31] Although pediatricians frequently provide antibiotics for asplenic patients younger than 2 years, the value of such an approach in older children and adults has not been adequately evaluated by clinical trial. Compliance is always a major problem with prophylactic programs.[1,2] In addition, pneumococci may become resistant to penicillin-type antibiotics, and other bacteria associated with OPSI are not sensitive to these drugs. Because cases of OPSI involving pneumococcal infection have been reported in patients who received both vaccination and penicillin prophylaxis, the use of prophylactic measures should never be allowed to result in a false sense of complacency.[32,33]

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